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TITLE: Psychosocial Stress and Ovarian Cancer Risk: Metabolomics and Perceived Stress

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14. ABSTRACT Mouse models suggest that chronic stress promotes ovarian tumorigenesis, but the relationship between stress and ovarian cancer has never been evaluated in humans. In our analysis of self-reported stress and risk of ovarian cancer, we noted that phobic anxiety and social isolation were suggestively associated with increased risk of ovarian cancer (hazard ratios of 1.14 and 1.24, respectively). Depression was significantly associated with increased ovarian cancer risk (hazard ratio: 1.26), as was being widowed (hazard ratio: 1.38). Taken together, these data are consistent with animal data demonstrating the adverse impact of chronic stress on ovarian cancer risk.					
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INTRODUCTION

The objective of this Ovarian Cancer Academy award is to take a multifaceted approach to studying the role of psychosocial stress in ovarian cancer risk. This study is being conducted in the Nurses' Health Studies (NHS and NHSII), two large prospective cohorts with about 1200 ovarian cancer cases between the two studies. In these two study populations, we have repeated questionnaires which have queried psychosocial stress, as well as pre-diagnostic blood specimens on 350 cases, and tissue blocks on 250 cases. The first specific aim of this application is to examine whether self-reported stress exposures (depressive symptoms, phobic anxiety, social support, job strain, care-giving stress) are associated with ovarian cancer risk. Also, in this aim, we will evaluate whether any associations are stronger for tumors which express the β_2 adrenergic receptors, as studies in mouse models have suggested that β_2 adrenergic receptor activation drives ovarian tumorigenesis. In the second aim, we will use metabolomic profiling of women with and without post-traumatic stress disorder (PTSD) to derive a signature of chronic stress and then apply that metabolomic stress signature to study women with and without ovarian cancer. As secondary aims, we will evaluate whether stress is more strongly associated with more aggressive tumors (defined by how quickly fatal the tumors are, and by likely tubal vs. ovarian origin) and will leverage the metabolomics data to query other potential pathways of interest, including lipid dysregulation.

KEYWORDS

Ovarian cancer, psychosocial stress, anxiety, depression, social support, metabolomics

OVERALL PROJECT SUMMARY

This grant began on September 30, 2013. Since the grant began, we have obtained IRB approval (Statement of Work [SOW] task 1a) and have performed statistical analyses of self-reported phobic anxiety, depressive symptoms, and social support (SOW task 1b). Analyses of self-reported job strain and care-giving stress have not yet begun, but are planned for early 2015. We have reported suggestive increases in ovarian cancer risk among women with high levels of phobic anxiety, women with depression, and socially isolated women, particularly widowed women, (see table 1 below), confirming that psychosocial stress may play a role in ovarian tumorigenesis.

In addition, we have completed construction of the tumor tissue microarray (TMA; SOW task 1c), stained for β_2 -adrenergic receptor expression (SOW task 1d) and have had the results read by our study pathologist (SOW task 1e). Analyses of the β_2 adrenergic receptor results will be completed by a doctoral student working with Drs. Poole (the principal investigator) and Tworoger (her DoD Academy mentor), planned for winter 2014.

These analyses were somewhat delayed because the original antibody chosen for the β_2 adrenergic receptor staining did not perform well in initial testing; we performed several experiments to optimize this antibody, but were unable to use this antibody. We subsequently identified a new antibody and optimized it, but this delayed our analysis of results.

For SOW task 2a, we have identified and selected plasma specimens from women with PTSD, women with trauma exposure, but who did not develop PTSD, and

women with no trauma exposure for developing metabolomic signatures of chronic stress. These samples will be aliquoted and shipped to the Broad Institute for metabolomics profiling in October 2014. We have additionally identified the cases and controls to be aliquoted for metabolomics profiling in the ovarian cancer case-control study. We originally planned to assay these women over the course of the grant, but, in working

Table 1. Association between self-reported psychosocial stress measures and risk of ovarian cancer in the NHS/NHSII		
Stress measure¹	Comparison	RR (95%CI)²
Phobic anxiety	Score 4+ vs. 0/1	1.14 (0.96, 1.36)
Depressive disorder	Yes vs. no	1.26 (1.02, 1.56)
Social isolation	Moderately isolated vs. socially integrated	1.24 (0.99, 1.56)
Marital status	Widowed vs. married	1.38 (1.11, 1.72)
¹ Phobic anxiety based on the Crown-Crisp scale; depression based on presence of depressive symptoms (from the Mental Health Index), use of anti-depressants, or report of physician-diagnosed depression; social support measured by the Berkman-Syme social network index		
² Relative risk (RR) and 95% confidence interval (CI) adjusting for age, known ovarian cancer risk factors, and cohort (NHS vs. NHSII)		

with Dr. Clary Clish, the director of metabolomics profiling at the Broad Institute, he informed us that the metabolomics assays are highly variable over time. Therefore, we have requested to change the protocol to assay all the women at once, rather than staggered over time.

For SOW task 5a, I have not yet begun coursework. Due to changes in course scheduling at the Harvard School of Public Health, the courses I originally planned to take during year 1 were not offered. Therefore, I plan to take Society, Human Development, and Health 254: Social Disparities, Stress and Health and Epidemiology 240: Use of Biomarkers in Epidemiologic Research in year 2 of the grant. With regards to task 5b, I meet weekly with Dr. Tworoger (my Academy mentor) and monthly with Dr. Kubzansky (a co-mentor on this project). I have not yet begun meeting with Dr. Quackenbush, as the informatics portion of the grant has not yet begun. For task 5c, I coordinate bi-weekly meetings of our internal Ovarian Cancer Analysis Group (OCAG) and have attended the regular bi-monthly meetings of the stress and cancer working group. For task 5d, I attended the Dana Farber/Harvard Cancer Center (DF/HCC) annual breast and gynecologic cancer retreat in March, 2014, the American Association for Cancer Research (AACR) annual meeting in April, 2014, and the DoD Ovarian Cancer Academy annual meeting (in conjunction with the Marsha Rivkin Ovarian Cancer Symposium) in September 2014.

KEY RESEARCH ACCOMPLISHMENTS

Below is a list of key research accomplishments in the first year of this award.

- Demonstration that self-reported psychosocial stress seems to be related to developing ovarian cancer, the first demonstration of this in humans (see Table 1).

CONCLUSION

Our analyses of self-reported psychosocial stress have demonstrated increased risk for ovarian cancer, consistent with data from animal studies. We will complete our analyses of additional self-reported stressors (job strain, care-giving stress) and evaluate whether the impact of stress seems to be through the β_2 adrenergic receptor. We will also develop a biomarker profile of chronic stress and evaluate whether this profile is a) associated with ovarian cancer risk and b) whether this profile illuminates the biologic pathways connected stress to disease.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

No publications have resulted from this project to date. However, the results of our analysis of phobic anxiety and ovarian cancer risk have been submitted to Psycho-Oncology, and provisionally accepted for a special issue on the role of stress and cancer (Poole EM, Kubzansky LD, Sook AK, Okereke OI, Tworoger SS. A prospective study of anxiety, as a marker of distress, and risk of ovarian cancer. Submitted to Psycho-Oncology, 2013.). A manuscript describing the role of depression in ovarian cancer risk has been completed and will be submitted in October, 2014 (Huang T, Poole EM, Okereke OI, Kubzansky LD, Eliassen AH, Wang M, Tworoger SS. Depression and Risk of Epithelial Ovarian Cancer.) Additionally, the results of the analysis of social support have been presented as an abstract at the Marsha Rivkin Ovarian Cancer Symposium (Poole EM, Kubzansky LD, Okereke OI, Tworoger SS. The impact of social isolation on ovarian cancer risk and survival.).

INVENTIONS, PATENTS AND LICENSES

Nothing to report.

REPORTABLE OUTCOMES

Nothing to report.

OTHER ACHIEVEMENTS

Nothing to report.

REFERENCES

Not applicable